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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/522,900	MCCORMICK ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-23,29,37-40 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-23,29,37-40 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4, 6-23, 29, 37-40 and 54 are pending.

Claims 5, 24-28, 30-36 and 41-53 have been cancelled.

Claims 1, 3, 6, 23 and 40 have been amended.

Claim 54 has been added.

2. Claims 1-4, 6-23, 29, 37-40 and 54 are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

5. The objection to the first line of the specification for not containing a priority statement is withdrawn in view of the amendments to the specification filed 11/17/2004.

6. The objection to claim 40 for not containing a hyphen or the term "to" between 0.1mg and 10mg is withdrawn in view of the amendment to the claim.

7. The rejection of claims 17-18 and 20-23 under 35 U.S.C 101 as being drawn to non-statutory subject matter as lacking the hand of man is withdrawn upon further consideration and in view of applicant's arguments.

8. The rejections of claims 1-23, 29 and 37-40, parts a, d and f only, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn

in view of the amendments to the claims, removing the term "derived" and for correcting the antecedent basis of the phrase "said polypeptide antigen" in claim 23.

9. The provisional rejection of claims 1-23, 29 and 37-40 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-23, 29 and 37-40 of copending Application No. 10/067,790 is withdrawn in view of the amendments to the claims and in view of the obviousness-type double patenting rejection set forth below (see item no. 21 below).

Response to Arguments

10. The rejection of claims 1-10 and 19 under 35 U.S.C 101 as being drawn to non-statutory subject matter as lacking the hand of man is maintained.

The response filed 11/17/2004 has been carefully considered, but is deemed not to be persuasive. The response states that the instantly claimed polypeptide self-antigen is different from naturally occurring polypeptides by at least feature (b) and (d) as recited in claim 1 as amended. In response to this argument applicant's claims are drawn to the polypeptide self-antigen, which includes an epitope of a surface immunoglobulin, which reads on the naturally occurring surface immunoglobulin as it exists naturally on B-cell lymphomas, independent of the method of its production. In view of the indefinite nature of the phrase "nucleic acid encoding a peptide sequence overlapping a peptide sequence encoded by said nucleic acid in the cells of said tumor of said subject" with a B cell lymphoma tumor, the phrase is interpreted as meaning the naturally expressed surface immunoglobulin in B cell lymphomas. There is nothing

recited in claim 1 that distinctly and particularly points out any non-naturally occurring differences between the instantly claimed polypeptide self-antigen and the surface immunoglobulin expressed in B cell lymphoma patients. With respect to feature (d) of claim 1, the claim does not require that the polypeptide self-antigen induce an immune response in the same mammal from which the polypeptide was obtained. Amendment of claim 1 to recite "An isolated" or "purified" polypeptide self-antigen or similar language would obviate this rejection.

11. The rejection of claims 1-4, 6-23, 29, 37-40 and applied to newly added claim 54 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

With respect to part b applied to claim 1 and those that depend from claim 1 (i.e., claims 2-4, 6-23, 29, 37-40 and newly added claim 54), the response filed 11/17/2004 has been carefully considered, but is deemed not to be persuasive. The response states that as presently amended, the claims are not indefinite as the minimal "part" is defined by feature (a) of claim1. In response to this argument, feature (a) of claim 1 does not particularly point out and distinctly claim which particular surface immunoglobulin epitope or epitopes are contemplated by the phrase and there can be many such epitopes. Claim 1 as written encompasses a polypeptide self-antigen that is encoded at least in part by a nucleic acid in the cells of a B-cell lymphoma, wherein the polypeptide includes a surface immunoglobulin epitope or epitopes. Thus, the claims

encompass a polypeptide self-antigen, which comprises an unidentified epitope or epitopes of a surface immunoglobulin and wherein unidentified parts of the polypeptide self-antigen are encoded in part by a nucleic acid in the cells of a B-cell lymphoma. It remains unclear what part or parts of the polypeptide self-antigen are encoded by a nucleic acid in the B-cell lymphoma cells, if any. The epitope or epitopes of a surface immunoglobulin include any fragments of the surface immunoglobulin, the fragments could be part of the constant region, part of the variable domain or domains or part of a CDR or CDRs or part of a framework or frameworks and any combinations thereof and the claim does not require that the nucleic acid from the B-cell lymphomas actually encode the epitope or epitopes referred to in part (a). Thus, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

With respect to part c, claim 1 and those that depend from claim 1 (i.e., claims 2-4, 6-23, 29, 37-40 and newly added claim 54), the response filed 11/17/2004 has been carefully considered, but is deemed not to be persuasive. The response states that the claims have been amended to clarify that the tumor is a B-cell lymphoma. In response, while this clarifies the particular type of tumor contemplated by the claims, it does not clarify the phrase "at risk of developing a [B-cell lymphoma] tumor, encoded at least in part by a nucleic acid in the cells of said tumor" because a person at risk of developing a B-cell lymphoma includes subjects that do not actually have B-cell lymphoma, and thus, if the tumorous cells do not exist, the nucleic acid encoding at least part of the polypeptide self-antigen, which is uniquely expressed in those tumorous cells also does not exist. Applicant did not address the question as to whether or not the polypeptide

self-antigen is encoded only in the tumor cells or if the polypeptide self-antigen with its unique epitopes is also expressed in a subject not having B-cell lymphoma (i.e., at risk of developing B-cell lymphoma). Applicant's arguments that the claims are not intended to encompass the general population is unpersuasive because applicant has not pointed to anything recited in the claims that defines the population intended and as discussed above a subject "at risk of developing B-cell lymphoma" encompasses the general population.

With respect to part e, the response filed 11/17/2004 has been carefully considered, but is deemed not to be persuasive. The response states the term "at least about" is a conventional U.S. patent claim term to designate a range with no upper limit and where the lower limit is about a given value and the response cites examples of recently issued patents that include the claim term "at least about". In response, the prosecution history of the cited patents is not at issue in the instant case and the examiner will not comment on the prosecution history in the cited U.S. Patents. However, in view of the art applied in the instant application (e.g., Hawkins et al) and the absence of a clear indication in applicant's specification as to what specific range of the administered polypeptide is covered by the term "about", the claim is indefinite. The court held the that claims reciting "at least about" were invalid for indefiniteness where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term "about." *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). (see MPEP 2173.05(b)).

12. The rejection of claims 1-4, 6-23, 29, 37-40 and applied to newly added claim 54 under 35 U.S.C. 112, first paragraph because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims is maintained (item no. 12 of the previous Office Action mailed 8/17/2004).

The response filed 11/17/2004 has been carefully considered, but is deemed not to be persuasive. The response states that the claims have been amended to recite that the polypeptide self-antigen contains an epitope from a B-cell lymphoma and may be used for B-cell lymphoma patients. Further, the response states that applicant has taken exception to the following statement made by the examiner "Thus, applicant is not enabled for any vaccine composition" and the response acknowledges that the literature shows many failed attempts at cancer vaccines, but notes that several compositions have shown positive results. In response, the literature showing both success and failures is evidence and only exemplifies the high degree of unpredictability in the art with respect to cancer therapy and ultimately, which cancer therapies can be predictably practiced with a reasonable expectation of success. It is noted that the instant claims are drawn to a B-cell lymphoma tumor specific "vaccine", which broadly encompasses preventing a B-cell lymphoma in subjects that do not yet have cancer, as well as completely curing cancer and preventing relapse. Further, applicants base claim, claim 1, recites a subject "at risk of developing a B-cell lymphoma tumor", which clearly encompasses treating a person who does not yet have cancer, as well as completely curing cancer and preventing any relapse. There is no teaching in the prior or post-filing

art or in applicant's specification indicating that B-cell lymphomas can be prevented or cured, thus indicating the high degree of unpredictability of preventing and curing cancer. In fact, a "vaccine" would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancerous cell including preventing genetic mutation, and immortalization. Thus, contrary to applicant's assertion, the instant specification does not enable such a "vaccine" for B-cell lymphomas.

13. The rejection of claims 1-4, 6-23, 29 and 37-40 and applied to newly added claim 54 under 35 U.S.C. 112, first paragraph because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims is maintained (item no. 13 of the previous Office Action mailed 8/17/2004).

The Examiner acknowledges that claims 12-16 were not included in the previous rejection, however, their exclusion was a typo as the issue under 35 U.S.C. 112, first paragraph remains the same. These claims depend from rejected claim 11 and do not resolve the instant enablement issue.

The response filed 11/17/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that while applicant's agree that the three-dimensional structure of the polypeptide antigen is probably important, the full set of CDRs may not be the critical feature. The response states that the critical feature is the linker and when the linker is changed the VL and VH are arranged differently and

induce a different immune response with many linkers rendering the molecule completely useless as a vaccine. The response continues by arguing that Benvenuti et al does not even consider the importance of the linker and Benvenuti et al does not indicate how many CDRs and what type are needed. In response to these arguments, while it appears that the linker is one critical feature of applicant's invention, complete VH and VL domains are also required. Applicant's claims still broadly encompass a polypeptide self-antigen that includes an epitope or epitopes of a surface immunoglubulin. Thus, applicant's base claim encompasses using any epitope(s) from the constant region or the hinge or the frameworks or the CDRs, which would not produce an idiotype that mimics the natural surface Ig expressed on B-cell lymphomas. Further, the claims encompass an idiotypic eptiope of a single V region, of any two V region domains (i.e., VH-VH), and of only part of the VH and only part of the VL domains, which encompasses incomplete VH and VL domains that do not contain the full complement of 6 CDRs, from both the heavy chain and light chain. Applicant has not provided any objective evidence that epitopes from the constant regions or hinge region or frameworks, or from a single V region, or from just any two V regions (i.e., VH-VH or VL-VL) or from only part of the VH and VL domains of B-cell lymphoma surface immunoglobulins result in conformational dependent epitopes (idiotypes) mimicking the surface immunoglobulins expressed on B cell lymphomas, which are complete immunoglobulins (i.e., comprise complete variable light and heavy chains as well as complete heavy and light constant regions). Further, applicant has not provided objective evidence that incomplete VH and VL scFvs connected via applicants linkers or

scFvs comprising two VH domains or two VL domains connected via applicant's linkers result in idiotypes that mimic the natural surface Ig expressed in B-cell lymphomas. Applicant acknowledges that the three-dimensional structure of the polypeptide self-antigen is probably important and as evidenced by applicant's own specification at page 45, lines 16-19, which states that the conformation of the relevant epitopes (idiotypes) in solution should resemble or mimic the same epitopes of the native protein as they appear on the surface of the tumor cell and at page 16 of the specification indicates that an idiotype is formed by the association of the hypervariable or complementary determining regions of VH and VL domains (see page 16 of the specification). It is unlikely that epitopes derived from any part of the surface immunoglobulin or epiotpes that do not contain complete VH and VL domains, which are incomplete structures would mimic the idiotypes of native surface immunoglobulins expressed in B-cell lymphomas. In fact, as evidenced by Casper et al (previously cited on PTO-892 mailed 8/17/2004), "a change of one or two amino acids in the second complementarity-determining region (CDR2) of the heavy chain seemed to be responsible for the loss of binding to the treatment of MoAb." (anti-idiotypic antibody) (see page 3699, left column). Thus, Casper et al teach that even minor structural changes (i.e., one or two amino acids) in a single CDR result in a structural change such that the idiotype of the surface Ig no longer resembles the original surface Ig expressed on B-cell lymphomas. Further, as pointed out by applicant Benvenuti et al makes clear that the immune response (i.e., anti-idiotypic antibodies) is directed exclusively against conformationally combined VL/VH determinants (see page 1557, right column), which further evidences that the

conformationally combined VH/VL pairs are required to mimic the natural idiotype of the surface immunoglobulin expressed in B-cell lymphomas. With respect to applicants arguments that Benevenuti et al immunize with naked DNA whereas the instant claims immunize with a polypeptide self-antigen, Benevenuti et al teach that anti-idiotypic antibodies are produced and directed exclusively against combined VH/VL determinants (i.e., idiotypes), which establishes that (a) the polypeptide is expressed and (b) the determinant or epitope (i.e., idiotype) is formed by the association of complete VH/VL pairs.

It is reiterated that applicant is enabled for a polypeptide self-antigen comprising both VH and VL domains, wherein the heavy and light chain CDRs are in their proper order and in the context of framework sequences, which maintain their required conformation and therefore, mimic the natural idiotype expressed on the surface of B-cell lymphomas.

14. The rejection of claims 1-4, 6-13, 17-22, 29, 38 and applied to newly added claim 54 under 35 U.S.C. 102(b) as being anticipated by Casper et al is maintained.

The response filed 11/17/2004 has been carefully considered, but is deemed not to be persuasive. The response argues the scFv of Casper et al is a fusion protein comprising GM-CSF. In response to this argument and as stated in the previous office action at page 16, applicant's claimed polypeptide self-antigen "includes...", which is equivalent to "comprising" and is inclusive or open-ended and does not exclude additional unrecited elements (see MPEP 2111.03). Therefore, the scFv-GM-CSF

taught by Casper et al reads on the claims. The response also argues that there is no assurance that the polypeptide is correctly folded or that the specific antigenic epitope is maintained and the data in figure 2 suggests that the GM-CSF protein portion fused to the scFv protein fused to the scFv is detrimental and the response speculates that the most likely reason being interfering with protein folding or blocking of the epitope. Applicant concludes that that the polypeptide-self antigen is not "in correctly folded form" as recited in claim 1, feature (c). In response to these arguments, applicant is reminded that all that is required is that the prior art set forth the substance of the invention. Casper et al teach a scFv-GM-CSF idiotype protein that induces an immune response, in fact, a significant and specific anti-Id immune response as shown in Figures 2 and 3, indicating that the scFv-GM-CSF is correctly folded, thereby mimicking the idiotype expressed by the natural surface Ig expressed in B-cell lymphomas. See also the text at page 3702, where Casper et al states "All mice developed a specific anti-Id immune response after vaccination".

Applicant also argues that claim 1, feature (d), indicates that the polypeptide "is capable of inducing an immune response in a mammal...without the need for adjuvant or other immunostimulatory materials" and the polypeptide taught by Casper contains a well-known material for enhancing the immune response. As pointed out in the previous office action the phrase "capable of" is non-limiting because an element "capable of" performing a function is not a positive limitation, but only requires the ability to so perform (page 16 of the previous Office Action). In response to applicant's argument, Casper et al teach that a scFv (adenovirus), which expressed a scFv (i.e.,

not fused or conjugated to another polypeptide) identical to the scFv (2A12) of the scFv-GM-CSF fusion, was capable of inducing an immune response as shown in Figures 2 and 3. Thus, the scFv lacking GM-CSF taught by Casper et al is capable of inducing an immune response without the need for adjuvant or other immunostimulatory materials and as such meets the requirement of claim 1, feature (d).

Applicant also argues that claims 2-4 provide for production of the claimed polypeptide in a plant and plant cells have a different physiology from animal cells and therefore, one may not assume that they will fold and process the polypeptide in the same manner as naturally occurs in human cells. In response applicant has not come forth with any evidence that the claimed polypeptide self-antigen is different from that in the prior art and applicant has not made any comparison between the claimed polypeptide self-antigen and that in the prior art to establish unexpected properties showing that the claimed polypeptide self-antigen is, in fact, different (see MPEP 2113).

15. The rejection of claims 1-4, 6-12, 17-23, 29 and 38 and applied to newly added claim 54 under 35 U.S.C. 102(b) as being anticipated by Hawkins et al is maintained.

The response filed 11/17/2004 has been carefully considered, but is deemed not to be persuasive. The response argues as above for Casper et al that there is no indication that the polypeptide is folded correctly or that it is capable of inducing an immune response without an adjuvant or immunostimulatory agent and the approach of using DNA vaccines lacks any suggestion of a correctly folded protein being produced because the scFv nucleic acid construct is artificial. In response to these arguments

and as pointed out in the previous Office action, Hawkins et al teach administration of the scFv generated a polyclonal anti-idiotypic antibody response, clearly indicating that the scFv was in correctly folded form and mimicked the natural surface Ig expressed in B-cell lymphomas (see pages 20-21). In response to applicant's arguments regarding the nucleic acid encoding the scFv (i.e., not fused or conjugated to another polypeptide), Hawkins et al teach that the polypeptide was expressed in vivo and produced anti-idiotypic antibodies that recognized the native Ig expressed on the surface of lymphoma cells (see pages 21-22). Thus, the scFv polypeptide is expressed in correctly folded form and is capable of inducing an immune response in the absence of an adjuvant or immunostimulatory agent.

The response also argues as above for Casper et al that claims 2-4 provide for production of the claimed polypeptide in a plant and plant cells have a different physiology from animal cells and therefore, one may not assume that they will fold and process the polypeptide in the same manner as naturally occurs in human cells. Again, as stated above, applicant has not come forth with any evidence that the claimed polypeptide self-antigen is different from that in the prior art and applicant has not made any comparison between the claimed polypeptide self-antigen and that in the prior art to establish unexpected properties showing that the claimed polypeptide self-antigen is, in fact, different (see MPEP 2113).

16. The rejection of claims 1-4, 6-23, 29, 37-40 and applied to newly added claim 54 under 35 U.S.C. 103(a) as being unpatentable over Casper et al in view of Fiedler et al and Tang et al and Hakim et al is maintained.

The response filed 11/17/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that all the arguments above regarding the deficiencies of Casper et al apply here as well and none of the secondary references compensate for the basic difference of not teaching a correctly folded polypeptide or a polypeptide capable of eliciting an immune response without an adjuvant or immunostimulatory agent. In response, the arguments presented above (see Casper et al) by the examiner apply here as well in that Casper et al teach that the scFv-GM-CSF elicits an anti-idiotype antibody immune response, which evidences that the polypeptide is in correctly folded form. Further, the scFv adenovirus construct of Casper et al expresses the scFv (not fused or conjugated to another polypeptide), which elicits an anti-idiotype immune response in the absence of an adjuvant or immunostimulatory agent and is thus, in correctly folded form.

Applicant also argues that the fact that the scFvs can be produced in plant cells and that these bind antigens does not demonstrate that they can induce an immune response in a mammal host, much less an immune response to treat a B-cell lymphoma. In response to this argument, as above Casper et al teach that the scFv can induce an anti-idiotypic immune response and a product and its properties are inseparable, regardless of the method of producing that product. As stated in the previous Office Action one of ordinary skill in the art would have been motivated and

had a reasonable expectation of success to produce the scFv of Casper et al in plants by the method of Fiedler et al because according Fiedler et al plant expression of scFvs eliminates the need for complex culture media, sterility or large culture vessels, possibility of composting plant waste material and no contamination with mammalian viruses or bacterial endotoxins, the latter two are especially important for producing scFvs for therapeutic use according to Fiedler et al. Further, one of ordinary skill in the art would have had a reasonable expectation of success because Fiedler et al teach the expression of a functional scFv in plants.

The response argues the Tang reference stating that the randomization process of Tang et al is performed differently and would produce a different result from applicant's present linker optimization. The response states that the linker of Tang et al is 18 amino acids long, being encoded by $(SNN)_{18}$ and is a truly random linker, whereas claims 14-16 provide for a repeated pattern of degenerate repeated triplet nucleotides with specific nucleotides at certain locations. In response to these arguments instant claim 14 is a linker from a randomized library of linkers that vary in size and sequence and the only requirement in claim 14 is that the trinucleotide does not contain the same nucleotide at all three positions (i.e., TTT) and claim 15 recites that the first two positions of the trinucleotide are selected from dA, dG, dC, dT. Thus, claims 14 and 15 are not limited to specific nucleotides at certain locations nor are they restricted to any particular size and as recited in claim 14 the linkers are from a randomized library of linkers. The features upon which applicant relies (i.e., non-random linkers) are not recited in the rejected claims. With respect to claim 16, the triplet (SNN) of Tang et al

wherein S is C or G and N is any nucleotide reads on the triplets GCT and GGT encompassed by claim 16.

The response argues that Hakim et al teach various proteins and peptide fused to scFvs to increase their immunogenicity, however, the instant invention adds immunostimulatory agents separately to the vaccine composition. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., administration of immunostimulatory agents separately) are not recited in rejected claims 1-23, 29 and 37-40. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

New Grounds of Objections/Rejections

17. The amendment to the first line of the specification filed 11/17/2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as

follows: The amendment claims priority to Application No. 60/155,979, filed on September 24, 1999, and incorporates the disclosure in its entirety by reference. The priority application cannot be incorporated by reference after the original filing of the instant application. This objection can be overcome by removing the incorporation by reference statement, thereby removing the new matter introduced therein.

See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application" (see Part VII).

Applicant is required to cancel the new matter in the reply to this Office Action

18. Claims 1-4, 6-23, 29, 37-40 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite for reciting "a nucleic acid encoding a peptide sequence overlapping a peptide sequence encoded by said nucleic acid in the cells of said tumor" in claim 1. It is totally unclear what peptide is encoded by the nucleic acid. Does the nucleic acid encode a peptide that shares only some sequence overlap with the encoded peptide in the cells of the tumor? What does the rest of the nucleic acid encode, some other protein not encoded in the tumor cells?

Claim 1 recites the limitation "said nucleic acid". There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites a nucleic acid that encodes, in part, a polypeptide self-antigen as well as a nucleic acid for producing the polypeptide self-antigen that encodes a peptide sequence that overlaps a peptide sequence of the

polypeptide self-antigen expressed in tumor cells. Is the nucleic acid encoding the polypeptide self-antigen expressed in tumor cells or is the nucleic acid the nucleic acid transformed or transfected in a cell or organism for producing the encoded polypeptide and do the two nucleic acids encode the same protein or just an overlapping peptide sequence?

19. Claim 54 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The response filed 11/17/2004 has introduced NEW MATTER into the claims. Newly added claim 54 recites that the polypeptide self-antigen of base claim 1 is not fused or conjugated to another polypeptide. The response did not point out where support for newly added claim 54 could be found in the originally filed disclosure. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP 714.02 and 2163.06 ("Applicant should therefore specifically point out the support for any amendments made to the disclosure."). Instant claim 54 now recites limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant

disclosure as filed. Such limitations recited in newly added claim 54, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in present claim 54 in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claim1-4, 6-23, 29, 37-40 and 54 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-40 of copending Application No. 10/067,790 in view of Hawkins et al (WO 94/08008, 4/14/1994, cited on PTO-892 mailed 8/17/2004).

The instant claims are drawn to a polypeptide self-antigen useful as a B-cell lymphoma tumor specific vaccine in a subject with a tumor or in a subject at risk of developing a tumor, wherein the polypeptide self-antigen: (1) includes a surface

immunoglobulin (surface Ig) epitope or epitopes unique to or over expressed by the tumor cells, (2) is produced in a cell or organism transformed by the nucleic acid, (3) is obtained from the transformed cell or organism in correctly folded form, and (4) the polypeptide self-antigen is capable of inducing an immune response in a mammal without the need for adjuvant or other immunostimulatory materials and the polypeptide self-antigen may not be fused or conjugated to another polypeptide (claim 54). Further, the polypeptide self-antigen has at least two peptide domains, includes at least one idiotypic epitope of the V region of said surface Ig, wherein there are at least two V regions of which at least part of the VH and VL are also domains of the said surface Ig, wherein the VH region has a CDR, which is CDR2, wherein the polypeptide is a two domain scFv that includes (i.e., comprises) VH and VL domains, wherein the VH and VL domains are linked by an amino acid linker between 1 and about 50 residues and facilitates the secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell or the linker connecting the VH and VL domains is a member of a randomized library of linkers with the following requirements: position 1 cannot be the same nucleotide as position 2 of a repeated triplet, position 2 cannot be the same nucleotide as position 3 of a repeated triplet, and position 1 cannot be the same nucleotide as position 3 of a repeated triplet (claim 14), wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of dA, dG, dC or dT (claim 15) and wherein the linker at position 1 is dA or dG, position 2 is dC or dG, and position 3 is dT (claim 16). Claim 23 recites wherein the administration comprises subcutaneous immunization with at least about 15 μg of said

polypeptide self-antigen three times about two weeks apart. Further, the polypeptide self-antigen is in solution, integrated into a carrier, induces a protective anti-tumor immune response, induces a polyclonal anti-idiotypic antibody response or a cell mediated immune response and wherein the antibody response is measured by testing serum or peripheral blood cells of the host in an enzyme immunoassay or by flow cytometry. Claim 29 is drawn to a vaccine composition comprising the polypeptide self-antigen (i.e., scFv) and a pharmaceutically acceptable carrier or excipient and further comprises an adjuvant, a, cytokine or a chemokine (claim 38), wherein the cytokine is selected from the group consisting of IL-1, IL-2, IL-12, IL-18 and IFN-γ. Claim 40 is interpreted as further limiting the vaccine composition, wherein the excipient is sterile saline and wherein each unit dosage is between 0.1 mg-10 mg of the polypeptide self-antigen.

Copending Application No. 10/067,790 is drawn to a polypeptide self-antigen essentially as described above for the instant claims. Claims 1-4 are broadly drawn to a polypeptide self-antigen as instantly claimed except the polypeptide self-antigen does not necessarily comprise epitopes from a surface immunoglobulin expressed on B-cell lymphomas. Claim 24 is broadly drawn to an individual-specific immunogenic product comprising the polypeptide of claim 13 (i.e., scFv idiotype wherein the VH and VL domain are linked via an amino acid linker having between 1 and 50 residues, consists of 12 different amino acids and facilitates the correct folding of the polypeptide to mimic the tumor epitope (i.e., surface Ig idiotype) in its native form on tumor cells). Thus, claims 1-4 and 24, in copending application no. 10/067,790 do not teach a polypeptide

self-antigen that includes epitopes of a surface immunoglobulin (i.e., idiotypes) that are useful as a B-cell lymphoma tumor specific vaccine. This deficiency is made up for in the teachings of Hawkins et al.

Hawkins et al teach polypeptide self-antigens comprising the VH and VL domains (i.e., scFv) of surface immunglobulins (i.e., idiotypic determinants) expressed on B-cell lymphomas (see entire document).

The claims in the instant application are obvious variants of copending Application No. 10/067,790 because it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced apolypeptide self-antigen that includes epitopes of a surface immunoglobulin (i.e., idiotypes) that are useful as a B-cell lymphoma tumor specific vaccine in view of Hawkins et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a polypeptide self-antigen that includes epitopes of a surface immunoglobulin (i.e., idiotypes) that are useful as a B-cell lymphoma tumor specific vaccine in view of Hawkins et al because Hawkins et al teach a polypeptide self-antigen that includes epitopes of a surface immunoglobulin (i.e., idiotypes) that are useful as a B-cell lymphoma tumor specific vaccine. Further, it is noted that claims 30-32 and 34-36 of copending application no. 10/067,790 merely recite inherent properties of the polypeptide self-antigen that are necessarily present in the vaccine composition comprising said polypeptide self-antigen.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

22. No claim is allowed.

23. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at

(571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER